IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION of
Ibrahim, et al.

Group Art Unit: 1655

Serial No.: 09/444,095

Examiner: Sisson, B.

Filed: November 22, 1999

FOR: Purification Method and Apparatus

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(Previously filed on March 7, 2001)
Compliance filed July 6, 2001 and
December 4, 2001)

AMENDMENT

Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

Responsive to the Notice of Non-Compliant Amendment dated November 27, 2001, 2001 and Office Action dated November 7, 2001, please enter the following amendments and consider the following remarks.

IN THE CLAIMS:

Please amend the claims as follows:

31. (Twice Amended) A method of DNA or RNA purification comprising:

placing a DNA or RNA containing sample in a first reservoir tube with a solution to effect release of DNA or RNA from cells in said sample,

inserting a wand into said first reservoir tube, wherein said wand comprises a cap, a sample collection assembly and an elongated shaft connecting said cap to said sample collection assembly, said sample collection assembly having microstructures for increasing the surface area of the sample collection assembly;

securely and sealingly closing said first reservoir tube with said cap of said wand with said shaft and said sample collection assembly inside said first reservoir tube;

agitating said first reservoir tube to mix said sample with said solution under conditions for releasing said DNA or RNA from cells in said sample and binding said

DNA or RNA to said sample collection assembly, thereby binding said DNA or said RNA to said sample collection assembly;

removing said wand from said first reservoir tube and inserting said wand into a second reservoir tube, said second reservoir tube containing a wash buffer;

securely and sealingly closing said second reservoir tube with said cap of said wand with said shaft and said sample collection assembly inside said second reservoir tube;

agitating said second reservoir tube to mix said sample with said wash buffer;

removing said wand from said second reservoir tube and inserting said wand into a third reservoir tube, said third reservoir tube containing an elution buffer;

incubating said third reservoir tube; and

recovering purified DNA or RNA from said third reservoir tube.

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65. (Amended) The method of claim 63, wherein said conditions for denaturing DNA or rendering RNA suitable for binding comprise: heating said reservoir tube to 95°C for a sufficient time to denature said double stranded DNA or render said RNA suitable for binding.

66. (Amended) The method of claim 63, wherein said microstructures comprise deep reactive ion etchings or toolings that provide an increased surface area on said sample collection assembly.

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67. (Amended) The method of claim 31, wherein said microstructures comprise deep reactive ion etchings or toolings that provide an increased surface area on said sample collection assembly.

REMARKS

Claims 31-35, 38, 39 and 63-67 are pending in the application. Claim 31 has been amended. Support for the amendments to the claims is found in the specification at page 3, line 21, page 4, line 3 from the bottom of the page, page 8, second paragraph-page 9,

page 10, lines 12-20, page 11, line 2. Applicants request entry of the above identified claims as they place the application in condition for allowance or better form for appeal.

Claims 31-35 and 63-67 have been rejected under 35 U.S.C.§112, first paragraph as allegedly not enabled. Applicant respectfully traverses this rejection.

Applicants will attempt to address the Examiner's comments one by one in the order in which they were recited in the Office Action.

The Examiner states:

That the claims are not enabled for sequence specific binding... and
Has sufficient breadth of scope so to encompass specific isolation/bindig of target nucleic acids or proteins to a solid support.

First of all, claims 31-35, 38 and 39 describe a device and a method for non-specific binding of nucleic acids. These claims contain the required steps involved and description of the invention sufficient to enable one skilled in the art to make and use the invention for isolating nucleic acids. As such, the Examiner even agrees with this on page 2 of the Office Action wherein the Examiner states that the claims are enabled for non-specific binding of nucleic acids or proteins. This is precisely what the claims are intended to address. Hence, claims 31-35, 38 and 39 are enabled under the requirements of section 112, first paragraph.

Applicant cannot understand how the Examiner raises the notion that claims 31-35 are somehow intended for binding of proteins or conducting an amplification reaction. This is not the case. Claims 31-35, 38-39 and 63-67 do not include any reference to protein binding or amplification. Applicant respectfully requests that some other invention not be read into the present claims that is not expressly stated in the claims.

Claims 63-67 are directed to sequence specific binding. The specification contains sufficient description on how to use the invention for specific binding of nucleic acids (DNA or RNA). The invention lies in the use of the novel apparatus in combination with the purification steps. Therefore, the present claims are supported by the original description. The claimed method including steps for non-specific and specific binding of nucleic acids are supported in the disclosure by incorporation by reference (see pages 8 and 9 of the disclosure) to prior methods of purification and also by the drawings of the

device. These references were intended to illustrate that the process of binding nucleic acids as well as other biological molecules to a solid support is well known in the art. In addition, some of the references listed were provided to the Examiner upon his request.

The Examiner further states:

"As set forth in the preamble of claim 31, the denaturing solution does not give rise to denatured nucleic acids, be they DNA or RNA. Yet, in order for one to selectively bind a probe to target nucleic acids, there needs to be a denaturation of the target nucleic acid such that it is single stranded prior to hybridization to the probe to the target."

This is not what the claim addresses at all. In claim 31, the denaturing solution is intended to denature a sample(s) to effect the release of DNA or RNA from cells. It is not intended to denature nucleic acids to bind to probes. Any person skilled in the art recognizes the distinction between denaturing a sample or denaturing nucleic acids. The aspect of the invention which deals with denaturing nucleic acids (not samples) and binding of nucleic acids to specific probes is set forth in claims 63-67, not claim 31. Applicants have requested amendment of claim 31 to simply state "solution" rather than "denaturing solution" so that there will not be any confusion.

The Examiner also states:

"The specification has been found to contain suggestions that the hybridization step can be conducted subsequent to having performed polymerase chain reaction. Neither the claims nor the specification teach how one is to perform such an amplification reaction when the nucleic acid is present in a protein denaturing solution. Clearly without something being done to the denaturation solution in which one finds the crude nucleic acid sample, the polymerase used to perform an amplification reaction would be rendered denatured as a direct result of such, be rendered inoperative."

Applicant requests that the Examiner point out where such suggestions are located that make these extrapolated implications to the claims? How did the Examiner come up with the idea that the invention suggested performing polymerase chain reaction in the presence of protein denaturing solution? Where was this stated? The claims do not suggest that the polymerase chain reaction could be performed in the presence of a protein denaturing solution. Such a basic fact is well known to any person of ordinary skill in the art. A description of a procedure to perform PCR amplification is not the subject of claims 31-35, 38-39 or 63-67.

The Examiner states in paragraph 3 of the Office Action that:

"Newly added claims 63-67 apparently seek to overcome some of the identified shortcomings identified in the prior Office action. However, the specification is essentially silent as to how the method is to be practiced. It is noted with particularity that the specification does not provide any example as to how such denaturation and annealing are to occur or to how prior art methods are to be adapted to the current method."

Claims 63-67 were added to substitute claim 36 in order to further clarify the distinction between specific and non-specific binding of nucleic acids and provide a description for each. The specification explicitly states that nucleic acids denaturation is performed by alkaline hydrolysis or heating, both methods are well known to any person skilled in the art. Therefore, Applicants submit that the description is accurate and complete under the requirements of section 112, first paragraph.

The Examiner further states in paragraph 3 of the Office Action that:

"Further, the claimed invention relates directly to matters of physiology and chemistry, which are inherently unpredictable and as such, require greater levels of enablement."

The invention does not relate to "physiology." Physiology is the science of studying the functions of organs, not purification of nucleic acids from samples. The voluminous articles in the literature clearly illustrate the predictability of the processes which deal with purification of nucleic acids from a sample, and hybridization of nucleic acids to sequence-specific probes. A list of the articles relating to such processes were submitted in the disclosure.

The Examiner states at paragraph 6 of the Office Action that:

At page 3 of the response received 25 September 2000 applicant directs attention to a number of publications and asserts that such documents are representative of the state of the art. The documents provided in the listing have not been considered on the record as they have not been provided on a PTO-1449 (Information Disclosure Statement) accompanied with the requisite certification and/or fee. Further, such documents, even if submitted, would not be considered as evidence of the state of the art as such do not take the form of a sworn declaration. Further, even if a sworn statement were to be provided that the cited documents are representative of the state of the art, the specification is still considered to be essentially silent as to how a skilled artisan would

adapt the prior art method to the manipulation and employment of the device required in the claimed methods."

The references cited in page 3 of the response received on 25 September 2000, namely, Ausubel F., Brent R., Kingston R.E., Moore D.D., Seidman J.G., Smith J.A., Struhl K., (1987). Current Protocols in Molecular Biology. Greene Publishing Associates and Wiley-Intersciences. John Wiley & Sons, New York, Chichester, Brisbane, Toronto, Singapore; Sambrook J., Fritsch EF, Maniatis J. (1989). Molecular cloning: A laboratory manual. 2nd edition, Cold Spring Harbor laboratory Press, Cold Spring Harbor, New York.) were listed in the disclosure (page 8). Additional references were also listed to illustrate that methods for capturing nucleic acids, proteins or cells either non-specifically or by affinity binding onto solid phase supports as well as detection by colorimetric, luminescent and fluorescent means are well known in the art. Those references are recognized and widely used by the artisan and the scientific community and many of which have already been adapted to purification and hybridization of nucleic acids on solid supports, a concept similar to the present invention.

Further, Applicant requests the Examiner to point out where in the MPEP or Rules the requirement is that references that have been incorporated by reference in the specification as indicative as the state of the art are not such if they are not cited in an IDS. Further, Applicants request that the Examiner cite authority showing that written publications are not indicative of the state of the art unless accompanied by a sworn declaration.

In paragraph 7 of the Office Action, the Examiner states:

"At page 4 of the response received 25 September 2000, it is asserted that the claims have been interpreted out of context and that the specification is enabling for claims 31-35. The above argument has been fully considered and has not been found to be persuasive toward the withdrawal of the rejection. As noted by the applicant in their response, the specification does make reference to modification and application of the method to additional embodiment including "incorporating thermal cycling amplification e.g., PCR), isothermal amplification and fluorogenic [sic], colorimetric, luminescent or electrochemical detection in the same device." While the claims are read in light of the specification, proffered limitations as to what the claims are not to encompass are not

read into the claims. It is noted with particularity that the method of claim 31 and by default, claims 32-35, 38, and 39 which depend therefrom, employ a "sample collection assembly" just as newly added claims 63 employs wherein the method of claim 63 (and dependent claims 64-67) is directed to '[a] method of capturing specific DNA or RNA."

Careful examination of the particularity of claims 31-35, 38-39 and 63-67, as well as the September 25, 2000 Response, makes it obvious that no references or specifications were made to perform amplification reactions or detection in these claims. It simply is not recited in the claims. A description of future adaptations of the device or methods is not the subject of these claims.

The Examiner state at the bottom of page 5 of the Action:

"Claims 31-35, like newly added claims 63-67, are not adequately supported by the disclosure to the context that one of skill in the art would be able to practice the full scope of the claimed method less resort to undue experimentation to do so."

Claims 31-35, 38-39 and 63-67 contain a sufficient description of the invention, and of the steps involved in using the invention to enable one skilled in the art to make and use the invention for isolating nucleic acids. The Examiner indicated on page 2 of the Action that the claims directed to non-specific binding nucleic acids were enabled. The description of the device and the steps for non-specific and specific binding of nucleic acids are supported by drawings of the device, which were provided in the original disclosure, and by references that illustrate the state of the art (see pages 8 and 9 of the disclosure). These references were intended to illustrate that the process of binding nucleic acids as well as other biological molecules to a solid support is well known in the art. Some of the references listed were provided to the Examiner upon his request. Therefore, Applicant maintains that these claims are enabled.

Claims 65-67 have been rejected under U.S.C. 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Applicant respectfully traverses this rejection.

The Examiner objects to the term "deep" in claims 66 and 67 as a relative term. Applicant submits that the term "deep reactive ion etching" is well known and defined in this field of engineering and is thus not ambiguous to one of ordinary skill in the art.

Claims 31-35 and 63-67 have been rejected under U.S.C. 112, second paragraph, as being allegedly incomplete for omitting essential steps, such omission amounting to a gap between the steps.

The Examiner states at page 7 of the Action that:

The omitted steps are: a. How the nucleic acid is to be prepared such that it is used in a hybridization reaction; b. If one is to conduct an amplification reaction, just how the amplification reaction is to be performed while there is a protein denaturant present (seemingly, the protein denaturant will result in rendering the polymerase inoperative). If one is to use a peptide probe after amplification, and the peptide probe is anti-histone antibody, the method needs to reflect what steps are needed so to render the amplified nucleic acid capable of being bound by the antibody, if such is even possible; and c. Like "b", supra, the use of a peptide probe, e.g., an antibody, to bind the nucleic acid, while the protein denaturant is present, raises several issues. The claims need to reflect just what steps are needed so to render the sample mixture susceptible to binding by another protein when the presence of denaturant would result in the denaturation of the peptide probe"

As stated in the 25 September 2000 Response, regarding a. above, a hybridization reaction is not the subject matter of claims 31-35. Thus, according to MPEP 2172.01, it is not necessary for the practice of the invention as set forth in these claims. However, a hybridization reaction would only be relevant for claims 63-67 if sequence-specific nucleic acids purification is desired. Such a procedure to prepare nucleic acids for hybridization is described in claims 63-67.

Regarding b. above, no suggestion was made to perform amplification reactions in the presence of denaturant in claims 31-35, 38-39 or 63-67, or anywhere else in the invention. Further, using a peptide probe or anti-histone antibody after amplification is not the subject of claims 31-35, 38-39 or 63-67.

Regarding c. above, claims 63-67 do not suggest using antibody or peptide probe in the presence of denaturant. The claims describe two alternatives for denature nucleic acids and allow hybridization of nucleic acids to a peptide nucleic acid probe (not an antibody) or oligonucleotide probe: alkaline hydrolysis or heating. If alkaline hydrolysis is used, then a neutralizing solution (Claim 64) should be added prior to bringing the probe and the nucleic acids in contact. If heating is used to denature the nucleic acids, then there is no need to add denaturing (alkaline) or neutralizing solutions. The nucleic acids and the probes are allowed to hybridize by gradual cooling of nucleic acids/probe mixture. Thus, there are no omitted steps.

The Examiner states on page 7 of *the Action:*
"At page 5 of the response it is asserted that "a hybridization reaction is not the subject matter of claims 31-35" and as such, no additional method steps are necessary. The above argument has been fully considered and has not been found to be persuasive to ward the withdrawal of the rejection."

Claims 31-35 do not recite hybridization. Hybridization reactions involving nucleic acids and probes are the subject of claims 63-67, not 31-35. Claims 31-35 describe non-specific purification of nucleic acids from cell sample(s) containing nucleic acids (DNA or RNA). The claim recites denaturing (i.e., lysing or breaking down the cell walls) a sample which contains DNA or RNA in order to release the DNA or RNA from the cells in the sample(s). It does not recite denaturing the actual DNA or RNA. Hybridization reactions are recited only under claim 63-67 if sequence-specific nucleic acids purification is desired. In such a case, the capture assembly can be coated with oligonucleotide or peptide nucleic acid probes of know sequence. The oligonucleotide probes can be used to capture rRNA, mRNA, total RNA, or single-stranded DNA molecules. In general, the capture of single stranded-DNA would require a step to render the double-stranded DNA into single-stranded DNA. This can be achieved by using an alkaline denaturing solution or by subjecting the purified DNA to heating for a sufficient amount of time to unwind the double-stranded DNA. Therefore, claims 31-35 are in compliance with the requirements of section 112, second paragraph.

Claims 31-35, 38, 39 and 63-67 are rejected under 35 U.S.S. 103(a) as being unpatentable over Ji et al., in view of Henco et al., Piasio et al., Lockhart et al., Tuunanen (WO 94/18564). Applicant respectfully traverses this rejection.

Ji et al. describes a triplex-mediated capture method for isolation of specific target tract from circular bacterial DNA using a specific oligonucleotide sequence and a solid support such as magnetic beads. The present invention is different in scope and content since we claim the use of an apparatus for purification of nucleic acids with or without knowing the target sequence. In addition, the present invention claims the use of a capture assembly that contains a wand and microstructures. The use of this capture assembly does not require use of magnetic field, filter paper, or column packing material (which requires gravitational or pressure forces) as required by Ji's invention. Therefore, Ji et al. does not render obvious the present invention.

Henco et al. discloses a device comprising a porous matrix bed in a column which contains silica gel or teflon particles. The use of such device requires pre-processing of the samples outside of the device, e.g., precipitation, aggregation or centrifugation. The process described by Henco et al. for immobilizing, washing and elution of DNA requires gravitational or pressure forces. In the present invention, the sample is processed in the device itself (the reservoir) without the need of centrifugation and does not require gravitational or pressure forces for washing or elution of the DNA. This is not taught or suggested by Henco et al. Hence, Henco et al. does not add to the teachings of Ji et al. to lead one of ordinary skill in the art to the present invention.

Piasio et al. describe a method and apparatus for conducting a chemical reaction, primarily of antigen-antibody nature, and colorimetric detection. Piasio et al. does not teach the use of the apparatus for purification of nucleic acids and does not teach other means of detection. The invention of Piasio et al. discloses a variety of solid support shapes which consist of a binding member and relatively large amount of surface area. The present invention provides significant improvements over Piasio et al., namely, the wider range of binding material which can be used (including silicon oxide, aluminum oxide or other zeolitic material); the presence of deep reactive ion etched microstructures (which provide vast or much increased surface area for far more efficient binding); and

the multipurpose utility (nucleic acids and protein purification, nucleic acids and proteins detection, and several means of detection, including colorimetric, fluorogenic and electrochemical methods). Thus, Piasio et al. does not add to the teachings of Ji et al. or Henco et al. to lead one of ordinary skill in the art to the present invention.

Lockhart et al. describe surface-bound, unimolecular, double-stranded DNA relating to the field of polymer synthesis and double-stranded oligonucleotide library screening. Lockhart et al. does not teach devices and methods for purification of nucleic acids. They only describe the unimolecular, double-stranded DNA. Lockhart et al. does not include any component similar to the claimed capture assembly, nor include the variety of materials that can be used with the claimed capture assembly, nor include the microstructure described in the claimed invention. Thus, Lockhart et al. does not make up for the deficiencies of the Ji, et al., Henco, et al., or Piasio, et al.

Tuunanen (WO 94/18564) discloses equipment and methods specifically for performing solid-phase immunoassays. The solid-phase support described by Tuunanen does not include microstructures or specific nucleic acid binding material. The increase in surface area created by protrusions, cavities or grooves, as shown in Tuunanen's figures and description is not comparable to the vast increase of surface area created by deep reactive ion etching or microparticles in the claimed invention. Unlike, the microstructures described in the claims, the grooves in Tuunanen are specifically described as leading downward to the point. The multiple washing description of Tuunanen relates specifically to the washing of an immunocomplex, not nucleic acids. Tuunanen does not provide the needed description to make up for the deficiencies of the Ji, et al., Henco, et al., or Piasio, et al.

In conclusion, none of the cited references, whether taken alone or in combination, would have lead one of ordinary skill in the art to the present invention because none of them provide a method for DNA or RNA purification that employs a wand having a sample collection assembly with microstructures of the type presently claimed. It should be apparent that the present invention offers many advantages over the prior art and presents several solutions to a myriad of problems. No single invention cited by the Examiner contains all the features claimed in the present invention in terms

of simplicity and adaptability. Further, none of the references provide the required motivation in the form of some statement or suggestion to make their combination as required by 35 U.S.C. §103(a) that would have lead one of ordinary skill in the art to the presently claimed invention. Therefore, the rejection under 35 U.S.C. §103(a) is believed overcome.

Reconsideration and allowance are respectfully requested. The Examiner is invited to telephone Applicant's representative at (301) 924-9500 if it would in any way expedite prosecution.

Respectfully submitted,

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